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HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	**Application No.** 10/682,230	**Applicant(s)** LAMB ET AL.	
	Examiner Zachary C. Howard	**Art Unit** 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *5,7,8,13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,9-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *10/9/2003*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

In the restriction requirement mailed 7/26/06, a new second election of species was required, consisting of parts (a) and (b). In the 1/22/07 response filed by Applicants, the following election of species was made:

(a) Applicants elect "upregulator" as the species of modulator; and

(b) Applicants elect "the small molecule having Formula VIII" as the single species of "upregulator".

Applicants do not indicate whether or not the species election is with or without traverse. However, because applicant did not distinctly and specifically point out the supposed errors in the requirement for species election, the species election has been treated as an election without traverse (MPEP § 818.03(a)).

On further consideration by the Examiner, part (b) of the species election is withdrawn. Part (a) of the species election is maintained for the reasons set forth previously and the claims will be examined as they read on the species of "upregulator".

In the 1/22/07 response, Applicants indicate that claims 1-4, 6, 9-12 and 14 are generic. The Examiner agrees and notes that even in view of the withdrawal of part (b) of the species election, each of claims 1-4, 6, 9-12 and 14 reads upon the elected species of "upregulator". However, claims 5, 7, 8, 13, 15 and 16 do not read upon the elected species of upregulator for the following reasons. The preamble of claims 5 and 13 indicates that each claim reads solely upon "inhibitors". Claims 7 and 15 are limited to TGF- β family members and claims 8 and 16 are limited to the cytokines IL-4, IL-10 and IL-13. The instant specification teaches, "immunosuppressive cytokines may also be used to modulate the Hedgehog signalling pathway. Examples include members of the TGF-β family such as TGF-β-1 and TGF-β-2, and interleukins such as IL-4, IL-10 and IL-13..." (pg 8, ¶ [0141]). The specification further teaches, "IL-10 and TGF-β down-regulate Shh expression" (pg 39, ¶ [0614]). Therefore, all of the species recited in claims 7 and 8 are "inhibitors". Therefore, claims 5, 7, 8, 13, 15 and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

It is noted that Applicants previously elected "Sonic Hedgehog" for the species of Hedgehog signaling pathway under consideration (this was the first election of species).

On the further consideration, the restriction requirement between Groups I and II is withdrawn, and the subject of these two Groups will now be examined together as Group I. Groups I and II include claims 1-16. The restriction requirement between Group I and Groups III and IV is maintained for the reasons set forth previously.

Claims 17-24 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/8/2006.

Claims 1-4, 6, 9-12 and 14 are under consideration, in so far as they read upon elected Group I (a method of modulating T-cell activation or proliferation comprising contacting T-cells with a modulator of a hedgehog signaling pathway or a modulator that is a target of the hedgehog signaling pathway) and (1) the species of "Sonic Hedgehog signaling pathway" and (2) the species of "upregulator".

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The executed declaration submitted by Applicants on 3/4/04 is defective because Jonathan Robert Lamb has signed a copy of the declaration but has not included a date of execution with the signature. It is noted that the copies of the declaration that were submitted on the same date were properly executed and dated by Gerard Francis Hoyne, Margaret Jane Dallman and Brian Robert Champion.

Specification

The disclosure is objected to because of the following informalities:

(1) The title of the invention, "HEDGEHOG", is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

(2) The disclosure is objected to because it contains embedded hyperlinks in paragraphs [0164]; [0166]; [0167]; [0181] and [0186]. Applicants are required to delete each embedded hyperlink. See MPEP § 608.01 (part VII).

(3) The Brief Description of Figure 5 on page 10 refers to "Figures 5A-5D" and then "5(A)", "5(C)" and "5(D). However, the corrected Figure 5 submitted by Applicants on 3/4/2004 contains parts 5A, 5B and 5C.

(4) The specification contains a Brief Description of Figure 24 on page 13. The specification on page 92, line 19, also refers to Figure 24. However, the Drawings submitted on 10/9/03 do not include a Figure 24. The last figure in the Drawings is Figure 23, and it is labeled "19/19" indicating that it is the last of 19 sheets submitted.

(5) The specification on page 95, line 16, refers to reference "(15)". The specification on pages 107-108 presents a list of references; however, these references are not numbered. It is unclear which reference is reference "(15)".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 9-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of upregulating T-cell activation, or proliferation, comprising contacting T-cells *in vitro* with anti-CD3 antibody, anti-CD28 antibody and the 19kDa N-terminal autoproteolytic Sonic hedgehog (Shh) peptide, does not reasonably provide enablement for a method of modulating T-cell activation or proliferation comprising contacting T-cells with a modulator of a Hedgehog signaling pathway or a modulator of a pathway which is a target of the Hedgehog signaling pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of modulating T-cell activation or proliferation by contacting T-cells with a modulator of a Hedgehog pathway. The elected species of Hedgehog pathway under consideration is the "Sonic hedgehog" pathway and the elected species of modulator under consideration is "upregulator".

The specification provides the following working examples in support of the claimed method. Examples 1-6 and 8-11 describe experimental materials and methods including mouse strains (Example 1); antibodies (Example 2); isolation of CD4+ T cells (Example 3); culture of CD4+ T-cells (Example 4); T-cell proliferation assays (Example 5); and immunocytochemistry (Example 6); statistical analysis (Example 8); RNA isolation (Example 9); reverse transcriptase PCR (Example 10) and real time PCR (Example 11). Examples 7 and 12-17 describe experimental results. Example 7 describes cell cycle analysis of CD4+ T-cells. Example 12 describes the expression of hedgehog signaling pathway components in resting and activated peripheral CD4+ T-cells and secondary lymphoid tissue. Example 13 demonstrates that the biologically active N-terminal Shh peptide increases T-cell proliferation (as measured by ^{3}H-thymidine incorporation) in purified peripheral CD4+ T-cells (Figures 7 and 19a) and

CD8+ T-cells (Figure 8) contacted with "sub-optimal" concentrations of anti-CD3 and anti-CD28 antibodies. This increase was not observed in either the absence of said antibodies or the presence of "optimal" concentrations of said antibodies (see pg 96 and Figure 19a). Example 14 demonstrates that the increase in T-cell proliferation in response to Shh is due to "promoted entry in the S/G2 proliferative phase" rather than increased cell survival. Example 15 demonstrates that anti-Shh antibody inhibits T-cell proliferation in CD4+ T-cells contacted with "sub-optimal" concentrations of anti-CD3 and anti-CD28 antibodies; the specification states that this demonstrates "that endogenous Shh is produced by activated CD4+ T-cells since the neutralizing antibody binds to Shh but not to the receptor, ptc" (pg 98, lines 27-29). Example 16 demonstrates that the anti-Shh antibody acts by blocking entry into the proliferative S/G2 phase of the cell cycle, rather than by decreasing cell survival. Example 17 describes a "kinetic analysis" of expression of several genes (including Shh, ptc, Gli1 and bcl-2) in activated CD4+ T-cells in the presence and absence of exogenous stimulated Shh.

In view of the teachings of the specification, and the teachings of the relevant art, the claims encompass the following embodiments for which the specification does not provide enablement:

(1) The claims encompass methods of upregulating T-cell activation, or proliferation, with Shh peptide alone (i.e., in the absence of anti-CD3 and anti-CD28 antibody). However, the specification teaches that addition of Shh protein alone to resting T-cells did not result in activation or proliferation (pg 96, lines 17-18; "No significant difference in the degree of proliferation was observed following the addition of the Shh peptide in resting CD4+ T-cells (Fig. 19A).") The addition of sub-optimal doses of both anti-CD3 and anti-CD28 were required for the Shh peptide to have a modulatory effect on the T-cell activation. The specification does not provide any guidance on how to use the Shh peptide as a modulator of T-cell activation in the absence of anti-CD3 and anti-CD28 antibodies, and it would require undue experimentation to determine how to use the Shh peptide in this manner.

(2) The claims encompass methods of upregulating T-cell activation, or proliferation, with upregulators of a Sonic Hedgehog (Shh) signaling pathway other than

the biologically active 19kDa N-terminal autoproteolytic Shh peptide. The claims encompass a vast genus of potential upregulators including compounds such as small molecules, proteins, nucleic acids, and more. However, the specification provides little guidance as to the nature of specific upregulators of Shh signaling pathway that can be used able to modulate T-cell activation or proliferation. The specification provides a single working example of an upregulator (19kDa N-terminal autoproteolytic Shh peptide) that works in the claimed method. The specification further teaches "Smo" and "Gli" as examples of agonist that are components of the Hedgehog signaling pathway. However, whereas Shh is a secreted protein, the Smo receptor is a membrane-bound protein and the Gli transcriptional regulator is a cytoplasmic protein. There is no working example of a method wherein T-cells are contacted with either the Smo receptor or the Gli protein that results in T-cell activation or proliferation. The specification further teaches that a large variety of small molecules that are "modulators" of the hedgehog signaling pathway (pages 38-51). However, there is no guidance provided by the specification as to which of these small molecules are upregulators and which are inhibitors. There is no guidance regarding the mechanism of interaction of these molecules with a Hedgehog pathway. Furthermore, there is no working example of a method wherein one of these putative Hedgehog signaling modulators is used specifically for T-cell activation or proliferation. The specification merely demonstrates that T-cells can be contacted with the Shh peptide to activate the T-cells, and then suggests that any agonist of a Shh signaling pathway can be used in a similar manner. In view of the breadth of the genus of upregulators encompassed by the claims and the minimal guidance regarding specific upregulators in said genus that will work to activate or proliferate T-cells, the claims lack enablement for the full scope of the claims. The specification merely invites the skilled artisan to screen compounds to identify upregulators of a Shh signaling pathway that can upregulate T-cell activation or proliferation.

(3) The claims also encompass methods of upregulating T-cell activation, or proliferation with upregulators of a pathway that is a target of the Shh signaling pathway. The specification contemplates both Notch and Wnt signaling pathways as

signaling pathways that are targets of a Hedgehog signaling pathway. The specification further teaches that "Gli acts on target genes wingless (Wnt)" ¶ [0112]. However, there are no working examples in the specification indicating that Wnt or Notch signaling pathways are targets of a Hedgehog signaling pathway in T-cells, either generally or specifically as part of activation or proliferation. While the Wnt gene has been shown to be a target of the Gli gene in some cell types, it is not predictable whether or not the Wnt gene is activated by the Gli gene as a part of T-cell activation. The Sonic hedgehog pathway does not necessarily activate an identical set of genes in every cell type. For example, the patched (Ptc) gene is generally activated by Gli in response to Hedgehog signaling (see page 18 of Cohen et al, 2003. American Journal of Medical Genetics. 123A: 5-28.) However, Applicants demonstrate that during T-cell activation that patched (Ptc) gene transcription is not activated. The specification teaches, "[a]ctivation of T-cells induced a sustained and marked (approximately 80-fold) increase in Shh mRNA, peaking at 44 and 72 hours. It lead to a downregulation of Ptc... Shh does not appear to affect Ptc downregulation" [0617].

Even if Wnt gene transcription was shown to be upregulated in conjunction with activation of a Shh pathway in activated T-cells, this would not indicate whether or not a modulator of the Wnt pathway could be used to modulate T-cell activation. The genus of potential upregulators of the Wnt pathway includes those acting through non-Hedgehog pathways such as the Wnt/β-catenin and Wnt/Ca^2+ pathways (see page 18 of Cohen, 2003; cited above). In order to use the claimed method the skilled artisan would first need to experiment to determine whether other upregulators of the Wnt pathway could be used for T-cell activation or proliferation

(4) The claimed method encompasses an *in vivo* method of modulating T-cell activation, or proliferation, with a modulator of Sonic Hedgehog signaling pathway or a modulator of a pathway that is a target of the Sonic Hedgehog signaling pathway. The specification teaches that the invention provides compositions for treatment of cancer, autoimmune diseases, lymphoproliferative disorders, psoriasis, atherosclerosis, restenosis, AIDS, immunodeficiency diseases, ischemic injuries, neurodegenerative diseases, osteoporosis, myelodysplastic syndromes, toxin-induced diseases, cachexia

and viral infections." (pg 1, ¶ [0006]). The specification does not provide any working examples wherein a modulator of a Shh signaling pathway (or target pathway) is administered to a subject for treatment. There are no working examples of modulation of *in vivo* T-cell activation or proliferation with said modulators. Furthermore, Sonic hedgehog signaling is involved in other *in vivo* processes related to thymocytes that may interfere with T-cell activation or proliferation. For example, Outram et al (2000) teaches that Shh inhibits thymocyte development in the DN (double negative) CD4-CD8- stage (see Outram et al, 2000. Immunity. 13: 187-197). In view of this teaching, the person of ordinary skill in the art could not predict whether or not administration of Shh or another modulator of a Shh signaling pathway would result in an increase, a decrease, or no effect on T-cell activation or proliferation. In view of this unpredictability, the skilled artisan would need to engage in undue experimentation to determine whether or not Shh, or another modulator of a Shh signaling pathway or another target pathway, could be used for any form of treatment.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how to make and use the full scope of the claimed methods of modulating T-cell activation or proliferation. The working examples related to modulation of T-cell activation or proliferation with anti-CD3, anti-CD28 and Shh are not commensurate in scope with the claimed methods, and the specification fails to provide guidance as to how to make and use the claimed methods over the full scope for the reasons set forth above. Due to the large quantity of experimentation necessary to determine how to use the claimed method (1) with an upregulator of a Shh signaling pathway in the absence of anti-CD3 and anti-CD28 antibodies; (2) with an upregulator of Shh signaling other than the 19kDa N-terminal autoproteolytic Shh peptide; (3) with an upregulator of a pathway that is a target of the Shh pathway; or (4) for *in vivo* treatment; the lack of direction/guidance presented in the specification regarding same, the lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4, 6, 9-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are genus claims because they are directed to methods of using a genus of modulator. The elected species of "modulator" under consideration is an "upregulator" of the "Sonic hedgehog" signaling pathway. The claims do not require the upregulator to possess any particular conserved structure. The claims only require that the upregulator (1) is able to upregulate the Sonic hedgehog pathway and (2) is able to modulate T-cell activation or proliferation.

Therefore, the genus of potential upregulators is highly variant because an essentially unlimited number of structural differences are permitted between genus members. Potential genus members include chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

However, while the claims encompass this vast genus of potential upregulators, the specification provides only limited description of upregulators of the Sonic hedgehog pathway that are able to modulate T-cell activation or proliferation. The specification describes the Sonic hedgehog protein as an upregulator of the pathway that can be used in the claimed invention. The specification further teaches "Smo" and "Gli" as examples of agonist that are components of the Hedgehog signaling pathway. However, while Shh is a secreted protein, the Smo receptor is membrane-bound and Gli is an cytoplasmic protein. There is no description of a method wherein T-cells are contacted with the Smo receptor or the Gli protein that results in T-cell activation or proliferation. Pages 38-51 provide a large variety of small molecules that are described as "modulators" of the hedgehog signaling pathway. However, there is no description of which of these small molecules are upregulators and which are inhibitors. There is no description of the mechanism of interaction of these molecules with the hedgehog pathway. Most importantly, there is no description of a method wherein one of these molecules is used for T-cell activation or proliferation.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of "upregulators" or the larger genus of "modulators". There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant upregulators are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method of modulating T-cell activation or proliferation comprising contacting T-cells with the 19kDa N-terminal autoproteolytic Sonic hedgehog peptide, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Gool et al, 1993. The Journal of Immunology. 150(8): 3254-3263.

Each of claims 1, 2, 4, 9, 10 and 12 encompasses a method of modulating T-cell activation (claims 1, 2 and 4) or proliferation (claims 9, 10 and 12) comprising contacting T-cells with an upregulator of a Hedgehog signaling pathway.

The instant specification teaches that when T-cells are contacted with sub-optimal doses of anti-CD3 and anti-CD28 antibodies, Sonic hedgehog (Shh) protein is secreted and is required for T-cell activation and proliferation (pg 98). Reduced T-cell activation and proliferation is observed when T-cells are contacted with sub-optimal doses of anti-CD3 and anti-CD28 antibodies in the presence of an anti-Shh antibody. This result demonstrates that T-cells activated by contact with sub-optimal doses of anti-CD3 and anti-CD28 antibodies secrete the Shh protein. Therefore, any prior art method of contacting T-cells with sub-optimal doses of anti-CD3 and anti-CD28 antibody would inherently result in "contacting T-cells with a modulator of a Hedgehog signaling pathway" because the T-cells would secrete and come into contact with the Shh protein.

Van Gool teaches contact of T lymphocytes with sub-optimal concentrations of anti-CD3 and anti-CD28. Van Gool teaches isolation of a population of T lymphocytes from blood that includes both CD4+ and CD8+ cells (pg 3255). Van Gool further teaches, "T lymphocytes were cultured during 3 days on plates coated with a suboptimal UCHT1 concentration (2.5 µg/ml)" (see Figure 2, legend). UCHT is an anti-CD3 monoclonal antibody (pg 3255, right column). Figure 2 indicates that the lymphocytes were also incubated with 200 ng/ml (0.2 µg/ml) of anti-CD28. The results shown in Figure 2 also indicate that the combined action of the two antibodies results in activation of the T-cells (as measured by cytotoxicity). Therefore, Van Gool teaches a method of contacting T-cells with sub-optimal does of anti-CD3 and anti-CD28 antibodies. While Van Gool did not appreciate that the activated T-cells secrete Shh as part of the activation process (and therefore contact Shh), this process would inherently occur in these cells as evidence by Applicants results described above. Therefore, the teachings of Van Gool anticipate instant claims 1, 2, 4, 9, 10 and 12.

Claims 6 and 14 each encompass an upregulator that is a "small molecule". The instant specification does not provide a limiting definition of the term "small molecule". The specification teaches "the modulator of the hedgehog signaling pathway may be a so-called "small molecule" agent, typically an organic molecule having a molecular weight of less than 2000 Da, preferably less than 1000 Da, suitably less than 500 Da. Many examples of such compounds are known in the art, for example as follows..." (pg 38, lines 16-20). However, this definition does not limit the claimed molecules to those smaller than 2 kDa; therefore the encompassed species include larger molecules (e.g., the 19 kDa Shh protein). Therefore, the term "small molecule" encompasses the Shh protein. Therefore, the method taught by Van Gool wherein the activated T-cells inherently secrete and are contacted by Shh protein also anticipates each of claims 6 and 13.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Outram et al, 2000. Immunity. 13: 187-197.

Each of claims 1, 2 and 4 encompasses a method of modulating T-cell activation comprising contacting T-cells with an upregulator of a Hedgehog signaling pathway. Each of claims 9, 10 and 12 encompasses a method of modulating T-cell proliferation comprising contacting T-cells with an upregulator of a Hedgehog signaling pathway. The recitation of "modulating T-cell activation" or "modulating T-cell proliferation" in the preamble of the claims from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. Furthermore, the specification provides no limiting definition of "T-cell activation" or "T-cell proliferation". Therefore, the claims have been interpreted as encompassing any method of "activating" a cellular process in T-cells comprising contacting T-cells with a modulator of Hedgehog signaling.

Outram teaches that a "neutralizing antibody against Shh accelerates thymocyte development in thymus explants" (pg 188). Outram teaches "culturing thymocytes with the anti-Hh neutralizing antibody 5E1" and "neutralization of Shh greatly increased thymocyte differentiation over this 3 day time period" and "there was a 2- to 3.5- fold increase in the number of thymocytes recovered from the cultures containing the neutralizing antibody" (pg 188-189). Therefore, Outram teaches a method of comprising contacting T-cells with a modulator of Hedgehog signaling and anticipates instant claims 1, 2, 4, 6, 9, 10, 12 and 14.

Claims 6 and 14 each encompass an upregulator that is a "antibody". Therefore, the method taught by Outram comprising contacting T-cells with anti-Shh antibody also anticipates each of claims 6 and 14.

Claims 1, 2, 4, 6, 9, 10, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al, December 2000. Immunology. 101(Supplement 1): pg 14. The publication date of Stewart (December 2000) is more than one year prior to the earliest U.S. filing date to which the instant application claims priority (4/9/02).

Each of claims 1, 2, 4, 9, 10 and 12 encompasses a method of modulating T-cell activation (claims 1, 2 and 4) or proliferation (claims 9, 10 and 12) comprising contacting T-cells with an upregulator of a Hedgehog signaling pathway.

Stewart teaches, "[w]e have studied the effects of a recombinant Shh peptide on human T cells. The addition of Shh enhances the proliferative response of both CD4+ and CD8+ cells following stimulation with αCD3 and αCD28" (pg 14). Therefore, Stewart teaches a method of modulating T-cell proliferation comprising contacting T-cells with Sonic hedgehog, an upregulator of a Hedgehog pathway. These teachings anticipate claims 9, 10 and 12. Furthermore, as stimulation with αCD3 and αCD28 inherently causes T-cell activation, the teachings of Stewart also anticipate claims 1, 2 and 4.

Claims 6 and 14 each encompass an upregulator that is a "small molecule". The instant specification does not provide a limiting definition of the term "small molecule".

The specification teaches “the modulator of the hedgehog signaling pathway may be a so-called “small molecule” agent, typically an organic molecule having a molecular weight of less than 2000 Da, preferably less than 1000 Da, suitably less than 500 Da. Many examples of such compounds are known in the art, for example as follows…” (pg 38, lines 16-20). However, this definition does not limit the claimed molecules to those smaller than 2 kDa; therefore the encompassed species include larger molecules (e.g., the 19 kDa Shh protein). Therefore, the term “small molecule” encompasses the Shh protein. Therefore, the method taught by Stewart also anticipates claims 6 and 14.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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